In vivo localisatie en kwantificatie van cerebrale dopamine receptoren

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SUMMARY

This Dutch thesis is based on a number of studies, which have been published in English-written professional journals. To offer more detailed information and in behalf of the foreign reader reprints of these publications have been added to this thesis (Appendices A upto E).

The principal question of the studies described within this thesis is what specific information can be derived from images as shown on page 1. On this picture the distribution of dopamine (DA) receptors in the living human brain has been visualized using a specific imaging technique: positron-emission tomography (PET).

This brief introduction is followed by a more extensive one (Chapter I). Aspects of the neurotransmitter system studied, the central dopaminergic (DA-ergic) system (I.1 and I.2), the role of this system in several disorders (I.4), as well as diagnostic methods used upto now (I.3) are reviewed. Partly due to its involvement in Parkinson's disease, the knowledge of the central DA-ergic system has assumed enormous proportions during the last 25 years. Most of it, however, is based on studies with experimental animals. For direct investigation of the system is hindered by its localization within the skull and behind the blood-brain barrier. The latter also hinders a directly verifying of the insights obtained from studies with animals, although postmortem obtained material often appears to be useful. Also the diagnostic methods used till now are indirect and often only indicate large defects, giving mostly no information about regional aspects i.e. the localization of the defect within the brain.

Next the principles are described of a number of non-invasive imaging techniques, that can make important contributions to brain research (I.5). Especially PET is very suitable by the combination of its relatively large spatial resolution with the fact that, provided that a good choice is made for the positron-emitting radiopharmaceutical, a tomogram can be obtained of all kinds of processes in the living brain at the molecular level. The various approaches in research of the cerebral DA-ergic neurotransmission using PET are reviewed (I.6). It appears that by far most studies are focused on visualizing specific elements of the DA-ergic neuronal system viz. the DA receptors.

After a short review of the performed studies (Chapter II, with reference to the Appendices already mentioned above) the introduction is followed by description and discussion of the most important results of the investigations (Chapter III). In all studies the rat was the experimental animal of choice. Tritium (^{3}H)-labelled spiperone, a DA and serotonin (5-HT) antagonist, and ^{3}H-NPA, a DA agonist, were used.

First, using a number of pharmacological criteria, the suitability of NPA for the *in vivo* radioactive labelling of DA receptors in the brain, was investigated. This appeared possible and optimal labelling conditions were established (III.1.2). Similar studies, using ^{3}H-spiperone, had already been published.

A method was developed for the rapid labelling of derivatives of the DA agonist ADTN with the positron-emitter carbon-11. From animal experiments these compounds appeared, however, to be not suitable for the *in vivo* labelling of DA receptors in brain (III.1.3).

Neuronal localization and identification of striatal DA receptors, labelled *in vivo* with ^{3}H-NPA or ^{3}H-spiperone, were determined (III.2). Using various lesioning techniques, different parts of striatal innervation were destroyed. Following tracer doses ^{3}H-NPA or ^{3}H-spiperone, these lesions appeared to have very different effects on striatal radioactivity accumulation, with both compounds. Removal of DA-ergic innervation led to higher striatal radioactivity levels in the lesioned structure following ^{3}H-NPA injection, while with ^{3}H-spiperone no differences were observed. Destroying striatal neurones (using kainic acid) led, in the lesioned striatum, to lower radioactivity accumulation following ^{3}H-NPA and higher following ^{3}H-spiperone.

These apparently paradoxical observations in the lesioned striata could be explained for both compounds by quantitative analysis of the dose-dependency of radioactivity accumulations (III.2 and III.4). From changes in receptor densities all striatal DA receptors that could be labelled *in vivo* with NPA, appeared to be localized postsynaptically. This was also found with spiperone. Nearly all (80%) DA receptors labelled with NPA were present on striatal neurones, the remaining on cortico-striatal projections. Of the DA receptors labelled with spiperone, also the major part (56%) appeared sensitive for kainic acid and a minor part (14%) disappeared after decortication. Part of striatal spiperone binding remained undefined. It is remarkable that the number of spiperone binding sites that disappeared was about twice that of NPA for both kainic acid and cortical lesioning.

In addition to the quantitative analysis of localization of *in vivo* NPA and spiperone binding, it has also been studied to what extent occupation of striatal DA receptors is coupled to biochemical effects (III.3). From these studies it has appeared that in the striatum an increasing occupation of DA receptors by NPA is not linearly correlated with (decreased) striatal DA metabolite (HVA and DOPAC) and (increased) acetylcholine (AcCh) concentrations. Striatal AcCh levels appeared to be inversely correlated with occupation of striatal DA receptors by spiperone.

From these investigations it is concluded that in the rat cerebral DA receptors can be detected *in vivo* with both radiolabelled NPA and spiperone. In both cases the postsynaptically localized DA receptor of the D-2 type is tagged. From the studies with lesions for both ligands neither qualitatively nor quantitatively correct information about the changes of receptor densities was obtained in the experiments using tracer doses. This finding may hinder direct "on screen" interpretation of PET images. To solve this problem the use of more intricated, computer-analyzed mathematical models in combination with studies at various doses, will be necessary.